RESPONSE

I. Status of the Claims

Prior to the Action, claims 3-12, 25, 29-31, 34-39, 41, 42, 46 and 47 were pending, of which the Office holds claims 36-39 to be drawn to initially non-elected species (**Section IV**). Presently, claims 48-51 have been added, which are fully supported by the claims and specification. No claims have been amended or cancelled.

Claims 3-12, 25, 29-31, 34-39, 41, 42 and 46-51 are therefore pending in the case. According to 37 C.F.R. § 1.121(c), a copy of the pending claims is provided in the amendment section.

II. Non-Rejected Claims

Applicants appreciate the indication that claim 10 is free from rejection on the basis of prior art and that claim 47 is free from rejection on the basis of prior art and enablement.

The rejection of claim 10 under 35 U.S.C. § 112, second paragraph is overcome by Applicants' response at **Section VII**, and the rejection of claim 10 under 35 U.S.C. § 112, first paragraph is overcome by Applicants' response at **Section VIII**. Accordingly, Applicants elect to submit claim 49, which places the subject matter of claim 10 in independent form, and is thus now allowed.

The only rejection of claim 47 is under 35 U.S.C. § 112, second paragraph in regard to the term "substantially", which is overcome by Applicants' response at **Section VII**. In this light, Applicants also elect to submit claim 50, which places the subject matter of claim 47 in independent form, and is thus now allowed.

All claims are anyway believed to be in condition for allowance in light of the present response and accompanying documents.

III. Support for the Claims

Support for the new claims exists in the current claims and throughout the specification and claims of the original and parent applications as filed. Any fee due for the new claims should be deducted from Peregrine Pharmaceuticals, Inc. Deposit Account No. 50-3493/ 3999.002587.

New claim 48 is a dependent claim based upon claim 10, but also including the term "or antigen-binding fragment thereof", which is derived from independent claim 5 and is supported thereby, in addition to throughout the specification and claims of the original and parent applications as filed.

New claim 49 is an independent claim directed to the subject matter of dependent claim 10, and is supported by claim 10 and claim 5, in addition to throughout the specification and claims of the original and parent applications as filed.

New claim 50 is an independent claim directed to the subject matter of dependent claim 47, and is supported thereby. Additional support exists in the specification, *e.g.*, at page 13, lines 12-13 and continuing thereafter, and in Example I, Example III and Example XIV.

New claim 51 is an independent claim directed to the subject matter of dependent claim 3, *i.e.*, wherein the immunoconjugate binds to VEGF bound to the VEGF receptor VEGFR1 on endothelial cells of the tumor vasculature and thereby localizes the immunoconjugate to the tumor vasculature. This is supported by claim 3 and claim 5, in addition to throughout the specification and claims of the original and parent applications as filed.

It will therefore be understood that no new matter is included in the new claims.

IV. Restriction and Species

The Action at page 2, Item 3, indicates that the earlier restriction requirement has been withdrawn. Applicants appreciate this holding.

Applicants confirm the species election of chemotherapeutic agent, as requested in the Action at page 3, Item 3.

Concerning the species election, the Action at pages 2 and 3, Items 1 and 3, states that claims 36-39 are "withdrawn from consideration as being drawn to a non-elected invention" (emphasis added). In fact, and as made clear in other portions of the Action at pages 2-3, Item 3, claims 36-39 are only drawn to initially non-elected species. These claims therefore remain pending in the case and can be rejoined upon allowability of generic, sub-generic and/or linking claims.

V. Amendment to Specification

The specification is presently being amended as requested in the Action at Item 4.

VI. Priority

The Action at pages 3-4, Item 5, appears to take the position that the present application is not entitled to a certain priority date due to perceived inadequacies in "prior-filed application, Application No. 09/508,251". However, as Applicants are not claiming priority to Application No. 09/508,251, the reference to this application is not understood[1].

[1] Although priority to April 28, 1999 is established by the present response and accompanying documents, should the Office wish to further question the priority date of the present application, the matter of the priority application and Application No. 09/508,251 will need to be clarified in a Non-Final Action.

The present application is entitled to the priority date of April 28, 1999. This is at least based upon the disclosure of 2C3 prodrugs in priority application Serial No. 60/131,432, filed April 28, 1999 ("the '432 application"; Attorney Docket No. 3999.002590), at pages 118-119[2].

The '432 application at page 118 begins by disclosing that the 2C3-based treatment methods of the invention "may be combined with any other methods generally employed in the treatment of the particular tumor, disease or disorder that the patient exhibits" and, in connection solid tumor treatment, "may be used in combination with classical approaches...". Thus, "to practice combined anti-tumor therapy, one would simply administer to an animal a 2C3-based construct in combination with another anti-cancer agent in a manner effective to result in their combined anti-tumor actions within the animal" ('432 application at page 118, emphasis added). Continuing at page 119, the '432 application discloses that "where 2C3-based immunoconjugates are used, various anti-cancer agents may be simultaneously or subsequently administered".

Notably, the '432 application at page 119 then refers to certain well known uses of combinations of substances in cancer treatment[2]. The first combinations mentioned are prodrugs, as exemplified by U.S. Patent No. 5,710,134 ("the '134 patent"; **Exhibit A**), which is incorporated by reference into the '432 application. The incorporated '134 patent provides additional enabling and written description support for the use of prodrugs with any antibody or immunoconjugate against VEGF and the VEGF receptor. Note, in particular, issued claims 2, 3, 4, 7, 9, 10, 13 and 14 in the '134 patent.

It has been established for many years that a patent need not teach, and preferably omits, what is well known in the art[2]. *Hybritech Inc. vs. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986). This applies equally to enablement and written description (*e.g.*, see Written

[2]See also, disclosure concerning anti-cancer prodrugs in general in priority application Serial No. 60/131,432, filed April 28, 1999, at page 35, lines 4-6 and page 120, lines 25-30.

Description Guidelines, *66 FR at 1105*, column 3, citing *Hybritech, supra*[3]). The Federal Circuit has emphasized this in several recent holdings, including *Amgen Inc. vs. Hoechst Marion Roussel Inc.*, 65 USPQ 1385 (Fed. Cir. 2003); *Capon vs. Eshhar vs. Dudas*, 418 F.3d 1349, 76 USPQ2d 1078 (Fed. Cir. 2005); and *Falkner vs. Inglis* (Fed. Cir. 2006, 05-1324).

Although the Federal Circuit stressed, in *Falkner vs. Inglis*, that incorporation by reference is not necessary to enable or describe components already known from accessible literature sources, it is also black letter patent law that issued U.S. patents can be incorporated by reference into a specification as an alternative to providing additional description of certain components of an invention. Thus, incorporation of the '134 patent, which claims tumor treatment methods using prodrugs with antibodies and immunoconjugates against VEGF and the VEGF receptor, into the '432 application clearly shows that the '432 application provides an effective priority date for the presently claimed invention. The present application is therefore entitled to the priority date of the '432 application, *i.e.*, April 28, 1999.

VII. Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

All examined claims are first rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Although Applicants respectfully traverse, the rejection is overcome.

A. Claim 9

Claim 9 is rejected as allegedly indefinite in reciting the phrase "chimeric antibody" (Action at page 5, Item 7). All other claims are free from this rejection.

The proper test of definiteness is whether, in the light of the teachings of the prior art and of the particular application disclosure, the claims set out and circumscribe, for one possessing an ordinary level of skill in the pertinent art, a particular area with a reasonable degree of particularity. *In re Moore*, 169 USPQ 236 (C.C.P.A. 1971).

---

[3]See also, *Falkner vs. Inglis* (Fed. Cir. 2006, 05–1324), discussed herein.

Although the Action alleges that the exact meaning of chimeric is not known, no support for such a position is provided. The rejection is thus *prima facie* improper. In contrast, the Action at page 5, Item 7, itself evidences understanding of the term. Those of ordinary skill in the art would likewise understand. That is all that is required to satisfy 35 U.S.C. § 112, second paragraph.

Moreover, Applicants' recent search identified over 600 issued U.S. patents, the claims of which also contain the term "chimeric antibody". Such routine issuance of the same claim term contradicts the Action's position that it is indefinite.

Finally, as the complained of term occurs in the same context in the claims issued in the parent, U.S. Patent No. 6,703,020 ("the '020 patent"), and related patents having the same specification, the rejections cannot be sustained. Note, for example, the '020 patent and U.S. Patent Nos. 6,342,219; 6,524,583; 7,056,509; 6,887,468; 6,342,221; 6,676,941; and 6,416,758 all contain the same claim language and are, by virtue of being issued U.S. patents, clearly definite. 35 U.S.C. § 282.

The rejection is thus overcome and should be withdrawn.

B. Substantially

All examined claims are rejected as allegedly being indefinite in regard to the term "substantially" (Action at page 5, Item 7). Again, the Action provides no reasoning in support of the rejection, which is thus *prima facie* improper. Applicants are also puzzled that the Action has questioned the clarity of the term "substantially" in the face of extensive case law showing the propriety of the term substantially and the standard use of this term in issued U.S. patents claiming prodrug technology.

By way of example only, in *Verve LLC vs. Crane Cams Inc.*, 65 USPQ2d 1051 (Fed. Cir. 2002), the Federal Circuit vacated a summary judgment that a patent was invalid for

indefiniteness based upon the failure of the specification and prosecution history to define sufficiently the claim term "substantially". The Federal Circuit held that expressions like "substantially" are used to accommodate minor variations appropriate to secure an invention. Thus, the term "substantially" is not indefinite when it serves reasonably to describe the scope of the subject matter. Commenting further:

> "Expressions such as 'substantially' are used in patent documents when warranted by the nature of the invention, in order to accommodate the minor variations that may be appropriate to secure the invention. Such usage may well satisfy the charge to 'particularly point out and distinctly claim' the invention, 35 U.S.C. §112, and indeed may be necessary in order to provide the inventor with the benefit of his invention. In *Andrew Corp. v. Gabriel Elecs. Inc.,* 847 F.2d 819, 821-22, 6 USPQ2d 2010, 2013 (Fed. Cir. 1988) the court explained that usages such as 'substantially equal' and 'closely approximate' may serve to describe the invention with precision appropriate to the technology and without intruding on the prior art. The court again explained in *Ecolab Inc. v. Envirochem, Inc.*, 264 F.3d 1358, 1367, 60 USPQ2d 1173, 1179 (Fed. Cir. 2001) that 'like the term 'about,' the term 'substantially' is a descriptive term commonly used in patent claims to 'avoid a strict numerical boundary to the specified parameter," quoting *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217, 36 USPQ2d 1225, 1229 (Fed. Cir. 1995).
>
> *Verve LLC vs. Crane Cams Inc.*, emphasis added.

The *Verve vs. Crane* decision is just one in a long line of cases from the Federal Circuit, its predecessor court and the Board, repeatedly holding that use of the term "substantially" does not render a claim indefinite. See *e.g., Andrew Corp. v. Gabriel Electronics*, 6 USPQ2d 2010 (Fed. Cir. 1988); *Seattle Box Co. v. Industrial Crating & Packing, Inc.*, 221 USPQ 568 (Fed. Cir. 1984); *In re Mattison*, 184 USPQ 484 (CCPA 1975); *Ex parte Smith*, 43 USPQ 157 (PTO Bd. App. 1937).

Even where the specification does not provide some standard for measuring the degree of a relative term, terms such as substantially are still definite so long as one of ordinary skill in the art would nevertheless be reasonably apprised of the scope of the invention in view of the knowledge in the art. *Seattle Box Co.* at 574. In the present case, it is clear that those of

ordinary skill in the art understand terms such as "substantially inactive prodrug" and "substantially active drug"[4]. Indeed, such terms routinely appear in the claims of issued U.S. patents in the prodrug field and are therefore *prima facie* definite. 35 U.S.C. § 282. For example, see U.S. Patent No. 6,538,039 (**Exhibit B**) and U.S. Patent No. 6,372,205 (**Exhibit C**), in which the claims recite "substantially noncytotoxic prodrugs", "substantially cytotoxic drugs" and "substantially inactive prodrugs".

In addition, § 112, second paragraph rejections over the term "substantially" were entered and overcome in several of the related patents having the same specification. Notably, these rejections were withdrawn after Applicants appealed during examination of the immediate parent application, now the '020 patent, and the related application that issued as U.S. Patent No. 6,342,221. Applicants include as **Exhibit D** a copy of the Appeal Brief submitted during examination of the parent application, which resulted in withdrawal of the § 112, second paragraph rejection over the term substantially.

The § 112, second paragraph rejections are thus overcome and should be withdrawn.

VIII. Rejection of Claim 10 Under 35 U.S.C. § 112, First Paragraph

Claim 10 alone is next rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enabling support in the specification. Although Applicants respectfully traverse, the rejection is overcome.

All claims other than claim 10 are free from this ground of rejection.

A. The Action's Assessment of Enabling Support

In terms of claim 10, the Action at page 6 first sets forth what is already agreed to be enabled, namely:

---

[4]The Action at pages 6, 7, 10-12 and 15 also evidences a clear understanding of the term "substantially inactive prodrug".

> "A method for treating cancer comprising administering to an animal a substantially inactive prodrug and a first immunoconjugate that comprises at least a first cleavage agent or enzyme operatively attached to at least a first anti-VEGF antibody, or antigen binding antibody fragment thereof, that binds to substantially the same epitope as the monoclonal antibody 2C3, wherein the immunoconjugates [*sic*] comprises variable regions that include the amino acid sequences of SEQ ID NO:7 or SEQ ID NO:9.

The Action at page 6 next sets forth what is allegedly lacking in enabling support, namely:

> "A method for treating cancer comprising administering to an animal a substantially inactive prodrug and a first immunoconjugate that comprises at least a first cleavage agent or enzyme operatively attached to at least a first anti-VEGF antibody, or antibody fragment thereof, that binds to substantially the same epitope as the monoclonal antibody 2C3, wherein the immunoconjugates [*sic*] comprises variable regions that include the amino acid sequences of SEQ ID NO:7 or SEQ ID NO:9.

Reviewing the Action's statements at page 6, it is evident that the only difference between what the Action agrees to be enabled and considers not to be enabled is the phrase "antigen binding" in terms of "an anti-VEGF antibody, or antigen binding fragment thereof". Such that use of "an anti-VEGF antibody or antigen binding fragment thereof" is enabled, whereas use of "an anti-VEGF antibody or fragment thereof" is said not to be enabled.

Irrespective, such reasoning does not support an enablement rejection of claim 10, as claim 10 does not include the only phrase giving rise to rejection, *i.e.*, "fragment thereof". Indeed, none of the claims include the complained of phrase "fragment thereof" without the accepted qualifier "antigen-binding". The independent claims in the case, claims 5, 46 and 49-51, each clearly recite "anti-VEGF antibody, or antigen-binding fragment thereof". This language therefore imparts to every dependent claim, which necessarily incorporate the limitations of the claim upon which they depend. 35 U.S.C. § 112, fourth paragraph; *Twin Disc Inc., v. U.S.*, 231 USPQ 417 (Cl. Ct. 1986). In any event, "fragment thereof" never occurs without "antigen-binding" in any dependent claim.

Thus, claim 10, and all other claims, already complies with the Action's assessment of enabling support and the rejection is consequently improper. Nonetheless, and without acquiescing with the present rejection in any way, Applicants have elected to add claim 48, which is based upon claim 10, but adds the enabling "antigen-binding" language from the Action at page 6.

B. Enablement, and Rejection Overcame in the Parent and Related Patents

As set forth above (**Section VII**), in addition to the immediate parent application, which issued as the '020 patent, the present application has the same specification as a number of other concurrently filed applications, which have now issued as patents. The '202 patent and U.S. Patent Nos. 6,342,219; 6,524,583; 7,056,509; 6,342,221; 6,676,941; and 6,416,758 each issued with claims containing the language now subject to rejection. U.S. patents are presumed valid under 35 U.S.C. § 282. Issuance of patents containing the same claim language from the immediate parent and related patents thus compels a finding of enabling support and patentability for the present claims. The Federal Circuit has held:

> "When multiple patents derive from the same initial application, the prosecution history regarding claim limitation in any patent that has issued applies with equal force to subsequently issued patents that contain same claim limitation".
>
> *Biovail Corp. International vs. Andrx Pharmaceuticals Inc.*, 57 USPQ2d 1813, 1816 (Fed. Cir. 2001).

As this application derives from the same initial application as the '202 patent and U.S. Patent Nos. 6,342,219; 6,524,583; 7,056,509; 6,342,221; 6,676,941; and 6,416,758, the Office's decision to issue the same claim language in the parent applications must be applied to claim 10 in the present application, which has the same limitations. Moreover, an analogous enablement rejection was entered and overcome in the parent application, prior to issuance of the '202 patent (see below).

The rejection is thus improper as being significantly at odds with decisions of the Office in the parent and related patents and should therefore be withdrawn.

C. The Rejection is Unfounded

Even without reference to the parent and related patents, the present rejection is anyway improper. According to established practice, the specification "*must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements". *In re Marzocchi & Horton*, 169 USPQ 367 (CCPA 1971), emphasis as in original. The Action does not present sufficient reason to doubt that the teaching of the specification enables the claims, particularly in the face of the well-established scientific field (see below).

In attempting to cast doubt on the specification, the Action at pages 6-7 first cites *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Importantly, in *Wands*, the Federal Circuit found sufficient enabling support for the claims at issue. In its decision overturning the Office's rejection in *Wands*, the Federal Circuit emphasized that the need for some experimentation was not a basis for a finding of non-enablement. 8 USPQ2d at 1406-7. In assessing the question of whether undue experimentation would be required in order to practice a claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (C.C.P.A. 1976). The need for some experimentation does not render the claimed invention unpatentable under 35 U.S.C. § 112, first paragraph. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

Continuing at page 8, the Action misinterprets claim 10 in important respects. Claim 10 recites that the antibody "comprises at least a first variable region that includes an amino acid

sequence region having the amino acid sequence of SEQ ID NO:7 or SEQ ID NO:9". The transitional phrase "comprising" means that the named elements are essential, but other elements may be added. *Genentech Inc. v. Chiron Corp.*, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997). Thus, the Action's reading of claim 10 as meaning only the Vh or Vκ regions, but not both, is inconsistent with standard claim interpretation rules, and claim 10 clearly covers antibodies comprising both Vh and Vκ regions.

Even as to an antibody containing only a Vh or Vκ region, without the other, the rejection is improper as it does not provide sufficient reason to doubt the specification and ignores the entire, and well-established field of single domain antibodies. The Action at page 8 alleges:

> "It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs, in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen-binding sites".

The Action cites no support for the foregoing position, which is contradicted by considerable scientific evidence (see below).

What the Action does cite at page 8 is the 1982 paper of Rudikoff *et al.*, *Proc. Natl. Acad. Sci. USA*, 79:1979-1983, 1982 ("Rudikoff"), which discusses the unremarkable concept that changes in amino acid sequences may in *some* situations alter antigen-binding specificity (emphasis as in original, see Rudikoff at abstract). There are several important points to note about Rudikoff and its irrelevance to the rejection of claim 10.

Firstly, Rudikoff concerns changes in amino acid sequences, whereas claim 10 recites "an amino acid sequence region having the amino acid sequence of SEQ ID NO:7 or SEQ ID NO:9", and thus does not concern amino acid changes. Secondly, and more importantly, Rudikoff was published in 1982, 17 years before this application's priority date, and now 24 years ago. To rely on a reference from 17 years before in an attempt to establish non-enablement stretches credibility to the limit. That is like attacking the PCR invention (1983) using a DNA amplification reference from 1966.

Thirdly, even if claim 10 concerned amino acid changes and Rudikoff was a contemporary publication, such a rejection would still ignore the considerable knowledge in the art, and the significant details in the specification, concerning how to prepare and test variant antibodies and antigen-binding regions.

In this regard, note that a similar enablement rejection was entered and overcame in the parent application, now the '202 patent. The Office rejected the same claims in the parent application, alleging that the specification did not reasonably enable antibodies and antigen-binding fragments that bind to substantially the same epitope as the 2C3 antibody (although antibodies containing only a Vh or Vκ region were not expressly discussed, the rejection was the same). The enablement rejection was withdrawn after Applicants filed the Appeal Brief of **Exhibit D**.

The remainder of the Action at pages 8-9 is particularly improper as it ignores the entire field of single domain antibodies, including all the patents and publications from the late 1980s to the present date. The present specification refers to "single domain antibodies (DABs)" at page 20, line 28, and such antibodies were routine at the time the invention was made. One of the first groups to coin the term "single domain antibodies or dAbs" was Greg Winter's group when, as early as 1989, they reported that isolated variable domains may offer an alternative to

monoclonal antibodies and serve as the key to building high-affinity human antibodies (Ward *et al.*, Nature, 1989, 341(6242):544-6, **Exhibit E**). This was followed by numerous publications from the early 1990s onwards (see **Exhibit F** for exemplary early abstracts).

The field today even includes two companies devoted to single domain antibodies, Domantis (**Exhibit G**, pages from Domantis website) and Ablynx (**Exhibit H**, pages from Ablynx website). The Domantis website confirms that high affinity single variable domains were first isolated by the Winter group in the late 80's, and continues to detail exemplary scientific publications in the field and several U.S. patents issued to Domantis (**Exhibit G**). Importantly, the Domantis website makes it clear that domain antibodies can correspond "to the variable regions of either the heavy (V_H) or light (V_L) chains of human antibodies" (**Exhibit G**, emphasis added). This alone disposes of the Action's unfounded allegation that single domain antigen-binding sites cannot be made or function.

The Ablynx technology is interesting for other reasons, as it concerns camelid antibodies, the antigen-binding site of which naturally has only a single domain (*e.g.*, Riechmann & Muyldermans, *J. Immunol. Methods.*, 231:25-38, 1999; Muyldermans *et al.*, 2001, *TIBS*, 26(4):230-235, 2001; **Exhibit I**). In addition to the V_H and V_L single domains of Domantis, the existence of the naturally-occurring single domain camelid antibodies also contradicts the Action's position that single domain antigen-binding sites cannot be made or function, as such antibodies have existed naturally for millennia.

The use of the camelised type of single domain antibody in real-world biotechnology also pre-dates the present application's priority date and was, at that time, already covered by the existence of issued U.S. patents. By way of example only, see U.S. Patent Nos. 5,759,808; 5,800,988 and 5,840,526 (**Exhibit J**). Note, also, the ongoing issuance of U.S. patents in this

field, such as U.S. Patent Nos. 6,005,079; 6,015,695; and 6,765,087 and the Domantis patents of **Exhibit G.**

A patent need not teach, and preferably omits, what is well known in the art (*Hybritech Inc. vs. Monoclonal Antibodies, Inc., supra*), and incorporation by reference is not necessary to enable components already known from accessible literature sources (*Falkner vs. Inglis, supra*). Accordingly, as single domain antibody technology was well-known when the present application was filed, there was no need for the application to include significant details on that subject. Presumably, this was recognized when the Office issued the eight earlier patents in the present portfolio.

The § 112, first paragraph rejection is thus overcome and should be withdrawn.

IX. Rejection of Claims 3-6, 8, 9, 11, 12, 25, 41, 42 and 46 Under 35 U.S.C. § 103(a)

Claims 3-6, 8, 9, 11, 12, 25, 41, 42 and 46 are further rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over Brekken *et al.*, *Cancer Res.*, 58:1952-1959, 1998 ("Brekken") in view of Melton & Sherwood, *J. Natl. Cancer Inst.*, 88:153-165, 1996 ("Melton") and Presta *et al.*, *Cancer Res.*, 57:4593-4599, 1997 ("Presta"). Although Applicants respectfully traverse, the rejection is overcome.

A. Claims Free From Rejection

Examined claims 10 and 47 are free from this ground of rejection. Independent claim 49, based on claim 10, and independent claim 50, based on claim 47, are thus also free from such a rejection[5]. Examined claims 7, 29-31, 34 and 35 are also free from this rejection, but subject to the second § 103(a) rejection set forth below.

[5]Should the Office wish to enter a § 103(a) rejection against claims 10, 47, 49 or 50, that would have to be made as part of a Non-Final Office Action, being a new ground of rejection not necessitated by Applicants' amendment or untimely submission of references.

B. Brekken is Not Available as Prior Art

As set forth above (**Section VI**), the present application is entitled to the priority date of the '432 application, *i.e.*, April 28, 1999. Brekken, which was published on May 01, 1998, is an article published on behalf of the present inventors less than a year before the present priority date. Brekken is thus only potentially available under 35 U.S.C. § 102(a) and can be removed as prior art by identifying the non-inventive contribution of the listed co-authors under *In re Katz*, 215 USPQ 14 (CCPA 1985).

Applicants therefore enter into the record a copy of the inventors' *Katz* declaration submitted in the parent application. The enclosed *Katz* declaration describes the non-inventive contributions of co-authors Xianming Huang and Steven W. King and explains that these individuals did not make an inventive contribution to the claimed invention, thus removing Brekken as prior art.

As Brekken is removed as prior art, any § 103(a) rejection relying on Brekken is *prima facie* improper and should be withdrawn.

C. The Rejection is Anyway Overcome

Even if Brekken was available as prior art, the § 103(a) rejection is still overcome for at least the following reasons and should be withdrawn.

For an obviousness rejection to be proper under 35 U.S.C. § 103(a), it is required that the cited prior art suggest to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and that the prior art also convey to those of ordinary skill a reasonable expectation of success. *In re Dow Chemical Co.*, 5 USPQ 2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *In re Dow Chemical Co., supra; In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

Before the Office may combine the disclosure of two or more prior art references in order to establish *prima facie* obviousness, there must be some suggestion for doing so, found either in the references themselves or in the knowledge generally available to one of skill in the art. *In re Fine*, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988); *In re Rouffet*, 47 USPQ2d 1453, 1456 (Fed. Cir. 1998). The burden is thus on the Office to establish the proper combinability of references. Moreover, a high level of skill in the art cannot be held to substitute for the required motivation to combine. *Rouffet* at 1458.

Brekken is cited as teaching the anti-VEGF antibody, 2C3, which blocks the interaction between VEGF and the VEGF receptor KDR/Flk-1 (VEGF receptor 2, VEGFR2) (Action at page 12, emphasis added). This is an important point, as will be developed below.

Presta is cited as concerning the anti-VEGF antibody A.4.6.1, and a humanized version, which are said to suppress VEGF-induced angiogenesis and tumor growth (Action at page 13, emphasis added). The function of the A.4.6.1 antibody is again important.

Brekken does not teach the use of 2C3 immunoconjugates with prodrugs (Action at page 12), neither does it suggest this. Likewise, Presta does not teach or suggest the use of A.4.6.1 immunoconjugates with prodrugs (Action at page 12).

Melton is cited as concerning antibody-directed enzyme prodrug therapy, ADEPT (Action at page 13). Melton does not teach or suggest the use of anti-VEGF antibodies in ADEPT.

Although the Action alleges that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine Brekken with Presta and Melton, such a position is in error. In contrast, the proposed combination is inconsistent with teachings of the references themselves and is thus legally improper.

Melton teaches that the antigen targeted by an ADEPT antibody should not circulate at high levels, as this will act as a competitor for antibody binding (Melton at page 154, bridging columns 1 and 2). This teaches away from the use of an anti-VEGF antibody in ADEPT, as abnormally high blood levels of VEGF were known to be associated with various cancers, including breast, gastric, lung and colorectal cancers. By way of example only, see Jinno *et al.*, *J. Gastroenterol.*, 33(3):376-82, 1998 (**Exhibit K**).

Essential components of the present rejection are the Action's characterization of Presta as concerning "VEGF-targeted antibody immunotherapy methods for the treatment of tumors" and Presta's success "in inhibiting tumor growth" (Action at pages 13 and 14). However, Presta does not concern any aspect of "targeted therapy", but is rather concerned only with the anti-angiogenic effects of the A.4.6.1 antibody (Presta throughout, *e.g.*, abstract, introduction, discussion). In fact, the effects of the A.4.6.1 antibody in inhibiting tumor growth are due to these anti-angiogenic properties. Anti-angiogenesis and tumor targeting are very different types of therapy though, and these modes of intervention cannot simply be interchanged, as attempted by the Action (for example, contrast the present application's introduction and summary, at pages 2-3 and 4).

Moreover, and as taught in the present specification, the A.4.6.1 antibody of Presta cannot be used as a targeting agent, as it binds to only to free VEGF and not to VEGF docked in any receptor. By providing an antibody that cannot be used in ADPET, Presta thus *teaches away* from the proposed combination with Melton, which combination is therefore improper. Similarly, by providing an antibody that only binds to free VEGF, Presta also *teaches away* from the presently claimed invention, which requires an antibody that can bind to VEGF when VEGF is itself bound to a receptor. Such teaching away in the art is clear evidence of patentability.

Mendenhall v. Astec Industries, Inc., 13 USPQ 2d 1913, 1939 (Tenn. 1988), *aff'd*, 13 USPQ 2d 1956 (Fed. Cir. 1989).

The rejection is not rescued by the addition of Brekken. The only binding property of the 2C3 antibody described in Brekken is that it blocks VEGF binding to the VEGF receptor KDR/Flk-1 (VEGF receptor 2, VEGFR2), as noted in the Action at page 12. Therefore, Brekken also fails to describe an antibody that can bind to VEGF when VEGF is bound to a receptor. This property, which is important for ADEPT, does not exist in the prior art, but is only provided by the present application. In particular, the present specification teaches:

> "A particular advantage of the present invention is that the antibodies provided inhibit VEGF binding only to VEGFR2, and not VEGFR1. This contrasts with the leading antibodies in the prior art, including A4.6.1, which inhibit VEGF binding to both VEGFR2 and VEGFR1...A further advantage is that, as binding of VEGF to VEGFR1 is maintained in the presence of the antibodies of the invention, they can be used to specifically deliver attached therapeutic agents to tumor vasculature by virtue of binding to VEGF that is bound to VEGFR1, which is upregulated on tumor endothelium. In the context of immunoconjugates, therefore, the present invention provides agents that have both anti-angiogenic and tumor destructive properties within the same molecule.
>
> Specification at page 4, lines 15-30, emphasis added.

The cited Brekken paper does not teach or suggest the foregoing important antibody property, which was not published until after the priority and subsequent applications were filed (Brekken *et al.*, *Cancer Res,* 60:5117-5124, September 2000).

As Brekken and Presta have been improperly combined with Melton, notably because Presta itself teaches away from the proposed combination, the § 103(a) rejection is unfounded and should be withdrawn. In any event, even if properly combined, the combination of Brekken, Presta and Melton still fails to teach or suggest the claimed invention and fails to provide a reasonable expectation of success. In particular, as neither Brekken nor Presta teaches or suggests the important antibody property, *i.e.*, that binding of VEGF to one VEGF receptor is

maintained, the combination of Brekken, Presta and Melton does not suggest the claimed invention and does not provide a reasonable expectation of success.

Although the rejection overall is overcome (and claims 49 and 50 are further removed from the rejection[5]), and without acquiescing with this rejection in any way, Applicants have elected to add claim 51, which even further distances the invention from Brekken, Presta and Melton, even if combined. Claim 51 emphasizes the use of an immunoconjugate that binds to VEGF bound to the VEGF receptor VEGFR1 on endothelial cells of the tumor vasculature, thereby localizing the immunoconjugate to the tumor vasculature, which is particularly lacking in the combination of the cited references.

In summary, the first § 103(a) rejection is thus overcome and should be withdrawn.

X. Rejection of Claims 5, 7, 29-31, 34 and 35 Under 35 U.S.C. § 103(a)

Lastly, claims 5, 7, 29-31, 34 and 35 are rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over the forgoing Brekken, Melton and Presta references in further view of U.S. Patent No. 5,863,538 to ("the '538 patent"; Attorney Docket No. 3999.000700) and U.S. Patent No. 5,621,002 ("the '002 patent").

A. Claims Free From Rejection

Examined claims 10 and 47 are free from this ground of rejection. Independent claim 49, based on claim 10, and independent claim 50, based on claim 47, are thus also free from such a rejection[5].

B. Brekken is Not Available as Prior Art

As set forth above (**Section VI**), the present application is entitled to the priority date of the '432 application, *i.e.*, April 28, 1999 and Brekken is not available as prior art (**Section IX**). As Brekken is removed as prior art, any § 103(a) rejection relying on Brekken is *prima facie* improper and should be withdrawn.

C. The Rejection is Anyway Overcome

Again, even if Brekken was available as prior art, the § 103(a) rejection is still overcome for at least the reasons set forth above in **Section IX**, which are specifically incorporated herein by reference. In particular, because Brekken and Presta have been improperly combined with Melton, and Presta itself teaches away from the proposed combination. Presta, which is essential to both § 103(a) rejections, in fact describes an antibody that is incapable of functioning as a vascular targeting agent, but acts only to bind free VEGF and to inhibit angiogenesis.

Thus, even if properly combined, the combination of Brekken, Presta and Melton fails to teach or suggest the claimed invention and fails to provide a reasonable expectation of success, particularly as neither Brekken nor Presta teaches or suggests the important antibody property that VEGF binding to one VEGF receptor is maintained. Neither the '538 patent nor the '002 patent cure such deficiencies and the rejection is thus improper.

The second § 103(a) rejection is thus overcome and should be withdrawn.

XI. PTO Form-892

Applicants note that the Presta reference, cited in the two § 103(a) rejections, was not listed on the PTO Form-892 included with the Action. Applicants therefore respectfully request that a new PTO Form-892 listing Presta be provided with the next communication from the Office.

XII. Conclusions

This is a complete response to the referenced Official Action. In conclusion, Applicants submit that, in light of the foregoing remarks and accompanying documents, the present claims are in condition for allowance and a timely indication to this effect is respectfully requested.

Should Examiner Joyce have any questions or comments, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

PEREGRINE PHARMACEUTICALS, INC.
Customer No. 000052101

Shelley P.M. Fussey, Ph.D.
Reg. No. 39,458
Agent for Applicants

5353 W. Alabama, Suite 306
Houston, Texas, 77056
(713) 439-0108

Date: September 13, 2006